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Research Article

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Phlebitis Induced by Intravenous Prostaglandin E1 in Patients with Malignancy Following Flap Reconstruction: A Case Series Study

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Abstract

Background: *Prostaglandin E1 (PGE1) is a vasodilator and smooth-muscle relaxant commonly used in patients with free flap reconstruction to increase the survival rate of the flap. However, phlebitis is the most common adverse event in patients who receive an intravenous solution of PGE1, and it will lead to more medical treatment.*

Objective: *The incidence of PGE1-induced phlebitis has not been well examined. This study aimed to determine which patient characteristics increase the risk of PGE1-induced phlebitis.*

Methods: *We retrospectively reviewed the medical records of patients with phlebitis caused by PGE1 in our hospital from May 2018 to May 2019. Among the records, we focused on patients with head and neck malignancy who received free flap reconstruction.*

Results: *In total, 1026 patients were prescribed PGE1, and 13 patients developed PGE1-induced phlebitis. Among 78 patients with head and neck cancer, the incidence rate of phlebitis was 15.4% (12 patients). These patients' mean age was 56 ± 9 years, and all were men. Their mean body weight, estimated glomerular filtration rate, serum creatinine level, white blood cell count, and neutrophil count were 69.6±12.6 kg, 81 ± 18 mL/min/1.73 m2, 0.97 ± 0.19 mg/dL, 10.3 ± 4.4 103/μL, and 75% ± 12%, respectively, before PGE1 administration. The white blood cell count before PGE1 administration was significantly higher ($p < 0.05$) in patients with phlebitis than in those without phlebitis.*

Conclusion: *Prescribers of PGE1 should be aware that patients with head and neck malignancy who receive flap reconstruction may have an increased risk of phlebitis. These patients should be monitored upon admission to prevent PGE1-induced phlebitis.*

Introduction

Microvascular free flap reconstruction is frequently used to treat head and neck defects [1, 2]. However, distal ischemia often occurs, and necrosis has become an important area of focus [3]. Several classes of drugs are prescribed for patients following flap reconstruction to improve flap survival. Among these, antiplatelet drugs, which inhibit platelet agglutination and thrombus formation, have been used as a first treatment for thrombotic complications [4]. Other options include prostaglandin and low-molecular-weight heparin [5, 6]. However, another study revealed that anticoagulation therapy did not significantly improve flap survival [7, 8].

Alprostadil (Prostaglandin E1) is a vasodilator and smooth muscle relaxant that is commonly used for flap survival in patients who undergo free flap reconstruction. A retrospective analysis revealed that thromboprophylaxis regime, such as prostaglandin, has a higher success rate with respect to preventing flap failure [9]. Prostaglandin E1 (PGE1) may cause side effects such as cutaneous vasodilation, edema, and phlebitis. Therefore, PGE1 is not the best treatment option for all individuals [10]. Nevertheless, some patients are still treated with PGE1 following flap reconstruction. Phlebitis is the most common adverse event in patients who receive an intravenous (IV) solution of alprostadil [11]. A

study reported alprostadil-induced phlebitis to be associated with pH. Therefore, alprostadil-induced phlebitis can be prevented by adjusting the pH of the IV PGE1 solution [12]. Moreover, the incidence of PGE1-induced phlebitis has not been well examined. Therefore, this study aimed to determine which patient characteristics increase the risk of PGE1-induced phlebitis.

Materials and Methods

Study Design and Participants

This retrospective study used the database of our hospital in Taiwan. Patients who developed PGE1-induced phlebitis at any time from May 01, 2018, to May 31, 2019 were enrolled. We also conducted causal inference through analyzing cases of phlebitis. This study was approved by the institutional review board of China Medical University Hospital (CMUH109-REC2-037).

Definitions of Phlebitis, Treatments and Comorbidity Assessments

According to the Infusion Nurses Society (INS), phlebitis is defined as the inflammation of a vein, and is graded from 0 to 4. Grades 0 to 4 refer, respectively, to no symptoms; slight pain or redness near the IV site; pain and redness near the IV site; pain along the cannula path, redness near the IV site, and swelling; and pain along the cannula path, redness near the IV site, swelling, and palpable venous cord [13].

We examined the clinical course through site observation following treatment. Physicians used the grading scale for phlebitis to determine the allocation of treatment. Treatment A was discontinuation of PGE1, treatment B was replacement of the IV site, and treatment C was replacement of the IV site and 7% NaHCO3.

To further determine patient-related characteristics that contributed to phlebitis, we compared patients' age, sex, body weight, and lab test results—which comprised estimated glomerular filtration rate (eGFR), serum creatinine (Cr), white blood cell (WBC) count, and neutrophil (Neu) level. In addition, several important risk factors were evaluated. We investigated comorbidities, including head and neck malignancy (ICD-10-CM codes C00–C10 and Z51), diabetes mellitus (ICD-10-CM codes C92 and Z51), and hypertension (ICD-10-CM codes I10–I13 and I15); concomitant drugs, including heparin, dextran, and glucose; and peripheral IV catheterization factors, such as needle catheter gauge, location of insertion, and rate flow.

Statistical Analysis

All data were analyzed using SPSS software. Descriptive statistics were used to summarize the basic characteristics. The characteristics were compared using the t test for continuous variables and the chi-squared test for categorical variables. A p value <0.05 indicated statistical significance.

Results

Participant Characteristics

To determine the cause of phlebitis in our hospital, we first reviewed patient medical charts and found that 1026 patients were prescribed PGE1 at any period between May 1, 2018, and May 31, 2019. The characteristics of the patients are presented in Table 1. PGE1 was prescribed by radiologists (55.4%), plastic surgeons (13.4%), and cardiologists (13.2%). Among the patients, 70% were men, and the average age was 62 ± 17 years. Most comorbidities were related to malignancy (50.2%), with liver tumor accounting for 41.7% and head and neck tumor accounting for 7.5%. Among the patients, 13 had IV PGE–induced phlebitis.

Table 1. Characteristics of patients prescribed with PGE1.

Case(n=1026)			
Demographic data		**No.**	**%**
Prescribers			
	Radiologists	568	55.4
	Plastic surgeon	137	13.4
	Cardiologist	135	13.2
	Other	186	18.1
Sex			
	Male	715	69.7
	Female	311	30.3
Average age (year± SD)		62.2± 17	
	Male	61± 16	
	Female	64.9± 19.9	
Comorbidities			
	Malignancy	515	50.2
	Liver	427	41.7
	Head and neck	78	7.5
	Connective & other soft tissue	2	0.4
	Gastrointestinal	2	0.4
	Stomach	1	0.1
	Renal	1	0.1
	Dermatologic	1	0.1
	Upper limb	1	0.1
	Ovary	1	0.1
	Breast	1	0.1
Diabetes mellitus		285	27.8
Hypertension		325	31.7

Patients with phlebitis induced by IV PGE1

The demographics of all the 13 patients with IV PGE1–induced phlebitis are shown in Table 2; these data were used to determine the clinical characteristics of these patients. Table 3 summarizes the characteristics of the patients upon admission: 12 patients (92.3%) had head and neck malignancy. All participants were male, and all received flap surgery for reconstruction. Their mean age was 56 ± 9 years, their mean body weight was 69.6 ± 12.6 kg, and their average alprostadil prescription duration was 4.4 ± 1.7 days. Regarding serostatus, the mean serum Cr level was 0.97 ± 0.19 mg/dL, eGFR was 81 ± 18 mL/min/1.73 m2, WBC count was

10.3 ± 4.45 103/μL, and Neu level was 75% ± 12%.

All patients received an isotonic infusion (5% glucose in 0.33% NaCl) with the same catheter gauge (20 G) and the same flow rate (20 mL/h). For eight patients (62%), the catheterization site was the dorsal aspect of the wrist, and for the remaining five patients (38%), the catheterization site was in the cubital fossa. Among these 13 patients, only nine (69%) received a pH adjustment for their infusion.

Table 2: Demographic and clinical information of 13 patients with PGE1-induced phlebitis.

Case	INS GRADE (Zero to four)	Age	Sex	Dose of PGE1 (mcg)/ day	7% $NaHCO^3$ (ml)	Concomitant medications		Primary disease	Flap for reconstr -uction	eGFR, mL/min /1.73m^2	Serum Cr, mg/dL	WBC, 10^3/μL	Neutr -ophils (%)	Treatment
						Heparin	Dextran							
1	1	60	M	100	0	2500IU	--	Malignant neoplasm of cheek mucosa	Yes	N/A	0.75	10	63.3	Treatment B
2	2	64	M	100	0	2500IU	20ml/hr	Malignant neoplasm of cheek mucosa	Yes	60	1.22	21.5	91.3	Treatment B
3	3	69	M	100	0	5000IU	20ml/hr	Malignant neoplasm of retromolar area	Yes	56	1.28	10.3	93.6	Treatment C
4	3	49	M	100	5	2500IU	20ml/hr	Malignant neoplasm of gum, unspecified	Yes	98	0.84	13.2	64.1	Treatment C
5	2	39	M	100	0	--	--	Malignant neoplasm of cheek mucosa	Yes	N/A	N/A	7.6	74.7	Treatment C
6	2	57	M	100	5	--	--	Malignant neoplasm of tongue, unspecified	Yes	90	0.88	4.8	N/A	Treatment B
7	2	51	M	100	5	2500IU	20ml/hr	Malignant neoplasm of lower gum	Yes	107	0.77	12.6	68.1	Treatment B
8	3	50	M	100	5	2500IU	20ml/hr	Malignant neoplasm of cheek mucosa	Yes	82	0.97	12.2	83.8	Treatment A
9	2	60	M	100	5	25000IU	20ml/hr	Malignant neoplasm of tongue, unspecified	Yes	97	0.81	8.5	60.7	Treatment B
10	3	69	M	100	5	---	20ml/hr	Malignant neoplasm of lower gum	Yes	57	1.25	9.8	86.1	Treatment B
11	2	62	M	100	5	---	20ml/hr	Malignant neoplasm of lower gum	Yes	78	0.97	N/A	73.2	Treatment A
12	3	43	M	100	5	25000IU	20ml/hr	Malignant neoplasm of connective and soft tissue of right lower limb, including hip	Yes	78	1.04	4.9	N/A	Treatment A
13	2	61	M	100	5	5000IU	20ml/hr	Malignant neoplasm of cheek mucosa	Yes	92	0.87	8.2	69.8	Treatment A

Patients received the following treatment options. Treatment A: discontinuation of PGE1; Treatment B: replacement of the IV site; Treatment C: replacement of the IV site with the addition of 7% NaHCO3. INS: Infusion Nurses Society; M: Male; PGE1: Prostaglandin

E1; ALT: Anterolateral Thigh; VL: Vastus Lateralis; Cr: Creatinine; eGFR: Estimated Glomerular Filtration Rate; WBC: White Blood Cell.

Table 3: Clinical backgrounds of 13 patients with PGE1-induced phlebitis.

Demographic data		N	%
	Age (year± SD)	56.5 ± 9.4	
	Sex, male	13	100.0
	Body weight (kg± SD)	69.6 ± 12.6	
Malignancy			
	Head and neck	12	92.3
	upper limb	1	7.7
Alprostadil (Days ± SD)		4.4 ± 1.7	
Blood and Urinary tests (mean± SD)			
	eGFR, mL/min/1.73m^2	81 ± 18	
	Serum Cr, mg/dL	0.97 ± 0.19	
	WBC, 10^3/μL	10.30 ± 4.45	
	Neu, %	75.34 ± 11.62	
Comorbidities			
	Diabetes mellitus	2	15.4
	Hypertension	3	23.1
Concomitant medications			
	Glucose 5% in 0.33% NaCl	13	100.0
	Heparin	9	69.2
	Dextran	10	76.9
Catheter gauge(G), 20G		13	100.0
5ml 7%NaHCO3			
	Yes	9	69.2
	No	4	30.8
First location of insertion			
	Dorsal aspect of the wrist	8	61.5
	Cubital fossa	5	38.5
Rate flow (20ml/hr)			
	Yes	13	100.0
	No	0	0.0

Data are expressed as mean ± SD or frequency.
Cr: creatinine; eGFR: estimated glomerular filtration rate; WBC: white blood cell; Neu: Neutrophil.
pH was adjusted by adding 7% $NaHCO_3$ to PGE1 solution.

Background Data Comparison of Patients with Head and Neck Malignancy with or without Phlebitis

A total of 1026 patients were prescribed PGE1, and 13 of these patients had phlebitis following flap reconstruction. We found that 78 patients had head and neck cancer, and the incidence rate of phlebitis was 15.4%. Therefore, among patients with head and neck tumors, we compared the clinical backgrounds of those with and without phlebitis. As shown in Table 4, the WBC count was

significantly higher in the phlebitis group than in the nonphlebitis group ($p < 0.05$).

Discussion

In this study, we demonstrated that PGE1-induced phlebitis in our institution was associated with particular patient characteristics, such as having received flap reconstruction. After a diagnosis of phlebitis, PGE1 treatment was discontinued in four patients (30.8%), the IV site was changed in six patients (46.2%), and both the IV site was changed and the infusion's pH was neutralized by an application of 7% NaHCO3 in the remaining three patients (23.0%).

As noted in previous studies, phlebitis has various risk factors, such as the IV site, infusion time, catheter gauge, patient's status, and pH and osmotic pressure of the solution [14-16].

Table 4: Comparison of the Background Data on Admission of Patients with Head and Neck Malignancy Who Received Pge1 with and Without Phlebitis.

Variable	phlebitis (n=12)		non-phlebitis (n=66)		p-value
	N	%	N	%	
PGE1 prescribers					
Plastic surgeon	9	75.0	60	90.9	0.49
Otorhinolaryngologist	3	25.0	5	7.6	
Radiologists	0	0.0	1	1.5	
Cardiologist	0	0.0	0	0.0	
Age (year± SD)	57± 8.8		56.7± 8.9		0.91
Sex, male	12	100.0	62	93.9	0.39
Body weight (kg± SD)	68.2± 12.4		65.8± 12.7		0.54
Alprostadil (Days ± SD)	4.5 ± 1.7		5.0± 1.7		0.32
Blood and Urinary tests (mean±SD)					
eGFR, mL/min/1.73m^2	81.7 ± 18.5		84.9± 24		0.69
Serum Cr, mg/dL	0.96 ± 0.20		0.96 ± 0.26		0.99
WBC, 10^3/μL	10.8 ± 4.3		7.6± 2.9		0.004
Neutrophils (%)	75.3 ± 11.6		68.6±11.4		0.08
Comorbidities					
Diabetes mellitus	2	16.7	10	15.2	0.80
Hypertension	3	25.0	23	34.8	0.63
Concomitant medications					
Glucose 5% in 0.33% NaCl	12	100.0	63	95.5	0.46
Heparin	7	58.3	51	77.3	0.17
Dextran	8	66.7	54	81.8	0.24
5ml 7%NaHCO3					
Yes	8	66.7	49	74.2	0.59
No	4	33.3	17	25.8	

Data are expressed as mean ± SD for variables and frequency (%) for nominal data. A result where $p < 0.05$ was considered significant. The t test was used to compare continuous variables and the chi-square test was used to compare categorical variables.

In vitro adjustment of the pH of the infusion prevented IV PGE1 induced phlebitis and venous pain [11, 12]. PGE1 is a slightly acidic solution (pH = 4.5–6.0), and $NaHCO_3$ can be used to neutralize the PGE1 solution. However, even if the solution was neutralized to a pH of 7.4 with 7% sodium bicarbonate, patients treated with PGE1 can develop phlebitis more frequently than has been reported, especially in male patients following free flap reconstruction. Among the 13 patients with phlebitis in this study, PGE1 was common used (92.3%) in flap reconstruction especially in head and neck malignancy patients.

In this study, the higher incidence of PGE1-induced phlebitis in patients with head and neck malignancy was due to the common use of peripheral IV PGE1 following flap reconstruction. These results suggest that patients with malignancy frequently have complex physical conditions and are prone to developing phlebitis

when treated with PGE1 because of their reduced resistance to chemicals.

Table 4 revealed that in patients with head and neck cancer in our hospital, in vitro adjustments to pH value, puncture site, infusion rate, infusion time, and catheter gauge do not significantly differ between those with and without phlebitis. The WBC count of patients with phlebitis was higher (mean: 10.9 ± 4.5 × 103/μL) than that of those without phlebitis. Two possible causes explain PGE1-induced phlebitis in patients with head and neck cancer who underwent flap reconstruction. First, PGE1 is commonly used in patients with head and neck cancer to improve the survival rate of flaps. Patients with immunodeficiency, such as those with burns or transplants, have weak blood vessels with low resistance to chemical stimulation [14-17]. Second, when the WBC count is slightly higher than the normal range, the patient is in an active inflammatory state and is prone to phlebitis [18, 19]. Phlebitis is frequently associated with the use of peripheral IV catheters, because IV catheters cause endothelial trauma and inflammation [18, 20]. However, the present study revealed that this risk factor did not differ significantly between malignancy patients with and without phlebitis.

Although this study offers valuable insights into PGE1-induced phlebitis in particular flap reconstruction patients, it had several limitations. First, the sample size was small, with only 13 cases in a single center in Taiwan. Second, hypotonic fluids, such as 5% dextrose, and infusion-related characteristics may have contributed to PGE1-induced phlebitis in some patients. Third, for patients with suspected phlebitis, clinical practices may result in patients' peripheral IV site being changed or replaced; this potentially contributed to an underestimation of the risk of phlebitis among patients who received PGE-1 following flap reconstruction. Hence, further studies with larger samples are necessary to determine the pathophysiology of PGE1 in head and neck free tissue transfer, in addition to the resulting phlebitis.

Conclusions

This study revealed PGE1-induced phlebitis was particularly prevalent in patients with head and neck cancer who underwent flap reconstruction. Moreover, patients treated with PGE1 tended to be those treated for flap survival and those with higher WBC counts; these patients also tended to have an increased risk of phlebitis. Clinicians who prescribe PGE1 should be aware that PGE1 may increase phlebitis risk for patients with malignancy who receive flap survival treatment. These patients should be monitored on admission to prevent PGE1-induced phlebitis. Further studies with larger samples are required to investigate PGE1-induced phlebitis in patients with head and neck flap reconstruction in Taiwan.

Ethics Statement: This study was approved by the institutional review board of China Medical University Hospital (CMUH109-REC2-037).

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